PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 06 January 2000 (06.01.00)	
International application No. PCT/US99/10619	**Applicant's or agent's file reference** 19113.0071/P
International filing date (day/month/year) 13 May 1999 (13.05.99)	**Priority date** (day/month/year) 15 May 1998 (15.05.98)
Applicant ARGRAVES, William, S. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

06 December 1999 (06.12.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Sean Taylor
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
NEEDLE & ROSENBERG, P.C.
Attn. MILLER, M.
1200 Candler Building
127 Peachtree Street
N.E. Atlanta GA 30303
UNITED STATES OF AMERICA

Applicant's or agent's file reference 19113.0071/P	Date of mailing *(day/month/year)* 18/10/1999
International application No. PCT/US 99/ 10619	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant MUSC FOUNDATION FOR RESEARCH DEVELOPMENT et al.	International filing date *(day/month/year)* 13/05/1999

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41–22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL–2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Authorized officer Sandra De Jong-van Dam

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
19113.0071/P		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 99/ 10619	13/05/1999	15/05/1998
Applicant		
MUSC FOUNDATION FOR RESEARCH DEVELOPMENT et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/10619

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/705 A01K67/027 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K A01K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BIRN, H., ET AL.: "Characterization of an epithelial {460-kDa protein that facilitates endocytosis of intrinsic factor-vitamin B12 and binds receptor-associated protein " THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 42, 17 October 1997 (1997-10-17), XP002117452 cited in the application the whole document --- -/--	1-3, 10-13, 18-25

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 October 1999	18/10/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Maddox, A

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	MOESTRUP, S.K., ET AL.: "The intrinsic factor-vitamin B12 receptor and target of teratogenic antibodies is a megalin-binding peripheral membrane protein with homolgy to developmental proteins" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 9, 27 February 1998 (1998-02-27), XP002117453 cited in the application the whole document	10-13, 20-25
X	BOND, H.M., ET AL.: "Characterization and purification of proteins which bind high-density lipoprotein" BIOCHEM. J., vol. 279, 1991, pages 633-641, XP002117454 the whole document	1,18-20
X	MATSUMOTO, A., ET AL.: "Cloning and characterization of HB2, a candidate high density lipoprotein receptor" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 27, 4 July 1997 (1997-07-04), pages 16778-16782, XP002117455 the whole document	10-15, 18,19, 22-27
X	MCKNIGHT, G.L., ET AL.: "Cloning and expression of a cellular high density lipoprotein-binding protein that is up-reglated by cholesterol loading of cells" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 267, no. 17, 1992, pages 12131-12141, XP002117456 WASHINGTON US the whole document	10-15, 19,22-27
X	WO 90 05744 A (UNIV WASHINGTON ;ZYMOGENETICS INC (US)) 31 May 1990 (1990-05-31) the whole document	1-15,18, 19, 22-27, 30,31, 33,34
X	SHEN, X.-Y., ET AL.: "Identification of high density lipoprotein binding proteins in mature adipocyte plasma membranes" BIOCHEMISTRY AND CELL BIOLOGY, vol. 71, no. 7/8, July 1993 (1993-07), pages 348-354, XP002117457 the whole document	19

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	TOZUKA, M., ET AL.: "Purification and characterization of two high-density-lipoprotein binding proteins from rat and human liver" BIOCHEM. J., vol. 261, 1989, pages 239-244, XP002117458 the whole document	19
X	FYFE, J.C., ET AL.: "Defective brush-border expression of intrinsic factor-cobalamin receptor in canine inherited intestinal cobalamin malabsorption" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 266, no. 7, 5 March 1991 (1991-03-05), pages 4489-4494, XP002117459 the whole document	16,28
A	VARBAN M L ET AL: "Targeted mutation reveals a central role for SR-BI in hepatic selective uptake of high density lipoprotein cholesterol" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 95, 1 April 1998 (1998-04-01), pages 4619-4624, XP002090830 ISSN: 0027-8424 the whole document	16,28
A	SAITO, A., ET AL.: "Complete cloning and seqeuncing of rat gp330/"megalin", a distictive member of the low density lipoprotein receptor gene family" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA., vol. 91, October 1994 (1994-10), pages 9725-9729, XP002117460 NATIONAL ACADEMY OF SCIENCE. WASHINGTON., US ISSN: 0027-8424 cited in the application the whole document	1,10-15, 20,22-27
A	WO 97 18304 A (MASSACHUSETTS INST TECHNOLOGY ;UNIV PENNSYLVANIA (US); UNIV TEXAS) 22 May 1997 (1997-05-22) the whole document	1-34

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	MURAKAMI, M., ET AL.: "Distinction in the mode of receptor-mediated endocytosis between high density lipoprotein and acetylated high density lipoprotein: evidence for high density lipoprotein receptor-mediated cholesterol transfer" THE JOURNAL OF BIOCHEMISTRY, vol. 101, 1987, pages 729-741, XP002117461 the whole document	1-34

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/10619

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9005744 A	31-05-1990	AU 642133 B	14-10-1993
		AU 4668589 A	12-06-1990
		CA 2003316 A	18-05-1990
		DK 94091 A	17-05-1991
		EP 0444154 A	04-09-1991
WO 9718304 A	22-05-1997	US 5925333 A	20-07-1999
		AU 1077497 A	05-06-1997
		CA 2240192 A	22-05-1997
		EP 0862625 A	09-09-1998

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

LEISSLER-GERSTL, Gabriele
EISENFÜHR, SPEISER & PARTNER
Arnulfstrasse 25
D-80335 München
ALLEMAGNE

EISENFÜHR, SPEISER & PARTNER
EINGEGANGEN/RECEIVED
17. Aug. 2000
MÜNCHEN
FRIST 31.8.2000

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	14.08.2000
Applicant's or agent's file reference: MM5077	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/10619	13/05/1999	15/05/1998

Applicant
MUSC FOUNDATION FOR RESEARCH DEVELOPMENT et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Vullo, C Tel.+49 89 2399-8061

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
MM5077		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/10619	13/05/1999	15/05/1998
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant MUSC FOUNDATION FOR RESEARCH DEVELOPMENT et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06/12/1999	14.08.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Paresce, D Telephone No. +49 89 2399 8995

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/10619

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-54 as originally filed

Claims, No.:

1-34 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4-9, 16-17, 28-32
	No:	Claims	1-3, 10-15, 18-27, 33-34
Inventive step (IS)	Yes:	Claims	
	No:	Claims	4-9, 16-17, 28-32
Industrial applicability (IA)	Yes:	Claims	1-34
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) The documents mentioned in this communication are numbered as in the search report, i.e. D1 corresponds to the first document of the search report.

2) **Novelty: Article 33(2) PCT**

The subject-matter of claims 1-3, 10-15, 18-27, 33-34 is not considered new in the sense of Article 33(2) PCT for the following reasons:

The present invention is based on the discovery of a mammalian receptor which binds and internalizes an HDL holoparticle. This receptor comprises a subunit of 450-600 kDa and one or more of the subunits selected from the group consisting of subunits of 40-50 kDa, 120 kDa, and 400 kDa. The 450-600 kDa subunit (which can also exist as a dimer of 800 kDa molecular weight) is the protein cubulin (present application p.4). Cubulin is a multifunctional receptor that has been described in the prior art.

D2 discloses the molecular characterization of cubulin, a rat 460 kDa epithelial glycoprotein that functions as the receptor facilitating endocytosis of IF-B12 complexes. D2 discloses the primary structure by cDNA cloning of cubulin. D2 mentions that cubulin may have other functions/ligands besides IF-B12. The receptor binds RAP and interacts with megalin (see p.5235 and p. 5238).

D1 describes the characterization of an epithelial 460 kDa protein that facilitates endocytosis of intrinsic factor-vitamin B12 (IF-B12) and binds RAP. This receptor was found to colocalize in renal and intestinal epithelium with the RAP and TC-B12 binding giant receptor, megalin. Megalin and cubulin colocalize in the endocytic apparatus (see figure 7). IF-B12 is internalized and directed to lysosomes for degradation of IF (see p.5240). The SDS-PAGE of the 460 kDa protein purified by IF-B12 affinity chromatography and immunoblotting with an anti-460 kDa protein monoclonal antibody shows, in addition to the 460 kDa protein a 800 kDa protein seen as a weak band under nonreducing conditions

(see figure 2 and p. 26500). It is suggested in D1 that the 800 kDa protein probably represents a disulfide-dependent dimerization of the 460 kDa protein. Furthermore, a 40-45 kDa protein was seen in some of the IF-B12 affinity preparations (see p. 26500). D1 also discloses that cDNA cloning of the protein will elucidate whether the protein has structural homology to other receptors, e.g. the low density lipoprotein receptor family proteins which also bind RAP (see p. 26504).

Therefore, both a 450-600 kDa subunit (as well as the cubulin dimer of 800 kDa molecular weight) and 40-50 kDa subunit of cubulin are disclosed in the prior art. The present invention is based on the discovery that these known receptors have the ability to bind and internalize an HDL holoparticle. However, the prior art receptors disclosed in D1 or D2 are prejudicial to the novelty of the receptor recited in present claims 1-3. The Applicant is informed that a statement of purpose, in a claim to a product may impose little or no limiting effect on the definition of the product as such. According to PCT Guidelines IV-7.6, a known product, which prima facie is the same as the substance or composition defined in the claim and is in a form suitable for the intended purpose (HDL receptor), though it has never been described for that use, would nevertheless deprive the claims of novelty. In addition several other receptors which specifically bind HDL have been disclosed in the prior art. For example,

D3 describes the characterization and purification of proteins which bind HDL. Membrane-associated proteins of 60, 85, 100 and 210 kDa had the ability to bind HDL in vitro. Furthermore, with gel filtration in octyl glucoside, a receptor complex was eluted with a molecular mass of 400-450 kDa (see p.1991).

D4 and D6 describe the cloning of a 110 kDa HDL binding protein and uses thereof. A 38 kDa protein that binds HDL is also disclosed (D6, see claims).

The subject-matter of claims 1-3, 10-15, 18-27, 33-34 is therefore, not considered novel.

The subject-matter of claims 4-9, 16-17, 28-32 has not been made available to the public by any of the available prior art documents and can therefore be regarded

as novel.

3) **Inventive Step: Article 33(3) PCT**

The subject-matter of claims 4-9, 16-17, 28-32 is not considered to involve an inventive step in the sense of Article 33(3) PCT for the following reasons:

D3 is regarded as being the closest prior art to the subject-matter of these claims.

As is discussed in paragraph 2) above, several receptors which specifically bind HDL have been disclosed in the prior art (see search report, D3-D7). Therefore, the problem underlying the present application has been identified as the provision of an alternative HDL-receptor. The solution to this problem is the provision of a receptor which comprises a subunit of 450-600 kDa and one or more of the subunits selected from the group consisting of subunits of 40-50 kDa, 120 kDa, and 400 kDa. The 450-600 kDa subunit (which can also exist as a dimer of 800 kDa molecular weight) is the protein cubulin (present application p.4). Cubulin is a multifunctional receptor that has been described in D1 or D2. D1 also discloses that cDNA cloning of the protein will elucidate whether the protein has structural homology to other receptors, e.g. the low density lipoprotein receptor family proteins which also bind RAP (see p. 26504).

The subject-matter of claims 4-9, 16-17, 28-32 consists in the provision of receptors comprising subunits of specific molecular weights that are slightly different from those of D3, D4, D5, D6 or D7 and methods of screening substances for the ability to modulate the HDL binding activity of said receptors. These variations are considered to come within the scope of the customary practice followed by persons skilled in the art. The receptors claimed in the present application can only be regarded as inventive, if the proteins presented unexpected effects or properties in relation to the other proteins disclosed in D3, D4, D5, D6 or D7. However, no such effects or properties are indicated in the application. Therefore, an inventive step for the claimed protein cannot at present be recognized, unless said protein will show some kind of unexpected advantages over those described in prior art, which should be demonstrated.

(see figure 2 and p. 26500). It is suggested in D1 that the 800 kDa protein probably represents a disulfide-dependent dimerization of the 460 kDa protein. Furthermore, a 40-45 kDa protein was seen in some of the IF-B12 affinity preparations (see p. 26500). D1 also discloses that cDNA cloning of the protein will elucidate whether the protein has structural homology to other receptors, e.g. the low density lipoprotein receptor family proteins which also bind RAP (see p. 26504).

Therefore, both a 450-600 kDa subunit (as well as the cubulin dimer of 800 kDa molecular weight) and 40-50 kDa subunit of cubulin are disclosed in the prior art. The present invention is based on the discovery that these known receptors have the ability to bind and internalize an HDL holoparticle. However, the prior art receptors disclosed in D1 or D2 are prejudicial to the novelty of the receptor recited in present claims 1-3. The Applicant is informed that a statement of purpose, in a claim to a product may impose little or no limiting effect on the definition of the product as such. According to PCT Guidelines IV-7.6, a known product, which prima facie is the same as the substance or composition defined in the claim and is in a form suitable for the intended purpose (HDL receptor), though it has never been described for that use, would nevertheless deprive the claims of novelty. In addition several other receptors which specifically bind HDL have been disclosed in the prior art. For example,

D3 describes the characterization and purification of proteins which bind HDL. Membrane-associated proteins of 60, 85, 100 and 210 kDa had the ability to bind HDL in vitro. Furthermore, with gel filtration in octyl glucoside, a receptor complex was eluted with a molecular mass of 400-450 kDa (see p.1991).

D4 and D6 describe the cloning of a 110 kDa HDL binding protein and uses thereof. A 38 kDa protein that binds HDL is also disclosed (D6, see claims).

The subject-matter of claims 1-3, 10-15, 18-27, 33-34 is therefore, not considered novel.

The subject-matter of claims 4-9, 16-17, 28-32 has not been made available to the public by any of the available prior art documents and can therefore be regarded

as novel.

3) **Inventive Step: Article 33(3) PCT**

The subject-matter of claims 4-9, 16-17, 28-32 is not considered to involve an inventive step in the sense of Article 33(3) PCT for the following reasons:

D3 is regarded as being the closest prior art to the subject-matter of these claims.

As is discussed in paragraph 2) above, several receptors which specifically bind HDL have been disclosed in the prior art (see search report, D3-D7). Therefore, the problem underlying the present application has been identified as the provision of an alternative HDL-receptor. The solution to this problem is the provision of a receptor which comprises a subunit of 450-600 kDa and one or more of the subunits selected from the group consisting of subunits of 40-50 kDa, 120 kDa, and 400 kDa. The 450-600 kDa subunit (which can also exist as a dimer of 800 kDa molecular weight) is the protein cubulin (present application p.4). Cubulin is a multifunctional receptor that has been described in D1 or D2. D1 also discloses that cDNA cloning of the protein will elucidate whether the protein has structural homology to other receptors, e.g. the low density lipoprotein receptor family proteins which also bind RAP (see p. 26504).

The subject-matter of claims 4-9, 16-17, 28-32 consists in the provision of receptors comprising subunits of specific molecular weights that are slightly different from those of D3, D4, D5, D6 or D7 and methods of screening substances for the ability to modulate the HDL binding activity of said receptors. These variations are considered to come within the scope of the customary practice followed by persons skilled in the art. The receptors claimed in the present application can only be regarded as inventive, if the proteins presented unexpected effects or properties in relation to the other proteins disclosed in D3, D4, D5, D6 or D7. However, no such effects or properties are indicated in the application. Therefore, an inventive step for the claimed protein cannot at present be recognized, unless said protein will show some kind of unexpected advantages over those described in prior art, which should be demonstrated.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
19113.0071/P		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 99/ 10619	13/05/1999	15/05/1998
Applicant		
MUSC FOUNDATION FOR RESEARCH DEVELOPMENT et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

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INTERNATIONAL SEARCH REPORT

[redacted]ational Application No
PCT/US 99/10619

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/705 A01K67/027 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K A01K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BIRN, H., ET AL.: "Characterization of an epithelial {460-kDa protein that facilitates endocytosis of intrinsic factor-vitamin B12 and binds receptor-associated protein " THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 42, 17 October 1997 (1997-10-17), XP002117452 cited in the application the whole document --- -/--	1-3, 10-13, 18-25

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 October 1999	18/10/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Maddox, A

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	MOESTRUP, S.K., ET AL.: "The intrinsic factor-vitamin B12 receptor and target of teratogenic antibodies is a megalin-binding peripheral membrane protein with homolgy to developmental proteins" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 9, 27 February 1998 (1998-02-27), XP002117453 cited in the application the whole document	10-13, 20-25
X	BOND, H.M., ET AL.: "Characterization and purification of proteins which bind high-density lipoprotein" BIOCHEM. J., vol. 279, 1991, pages 633-641, XP002117454 the whole document	1,18-20
X	MATSUMOTO, A., ET AL.: "Cloning and characterization of HB2, a candidate high density lipoprotein receptor" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 27, 4 July 1997 (1997-07-04), pages 16778-16782, XP002117455 the whole document	10-15, 18,19, 22-27
X	MCKNIGHT, G.L., ET AL.: "Cloning and expression of a cellular high density lipoprotein-binding protein that is up-reglated by cholesterol loading of cells" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 267, no. 17, 1992, pages 12131-12141, XP002117456 WASHINGTON US the whole document	10-15, 19,22-27
X	WO 90 05744 A (UNIV WASHINGTON ;ZYMOGENETICS INC (US)) 31 May 1990 (1990-05-31) the whole document	1-15,18, 19, 22-27, 30,31, 33,34
X	SHEN, X.-Y., ET AL.: "Identification of high density lipoprotein binding proteins in mature adipocyte plasma membranes" BIOCHEMISTRY AND CELL BIOLOGY, vol. 71, no. 7/8, July 1993 (1993-07), pages 348-354, XP002117457 the whole document	19

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	TOZUKA, M., ET AL.: "Purification and characterization of two high-density-lipoprotein binding proteins from rat and human liver" BIOCHEM. J., vol. 261, 1989, pages 239-244, XP002117458 the whole document	19
X	FYFE, J.C., ET AL.: "Defective brush-border expression of intrinsic factor-cobalamin receptor in canine inherited intestinal cobalamin malabsorption" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 266, no. 7, 5 March 1991 (1991-03-05), pages 4489-4494, XP002117459 the whole document	16,28
A	VARBAN M L ET AL: "Targeted mutation reveals a central role for SR-BI in hepatic selective uptake of high density lipoprotein cholesterol" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 95, 1 April 1998 (1998-04-01), pages 4619-4624, XP002090830 ISSN: 0027-8424 the whole document	16,28
A	SAITO, A., ET AL.: "Complete cloning and seqeuncing of rat gp330/"megalin", a distictive member of the low density lipoprotein receptor gene family" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA., vol. 91, October 1994 (1994-10), pages 9725-9729, XP002117460 NATIONAL ACADEMY OF SCIENCE. WASHINGTON., US ISSN: 0027-8424 cited in the application the whole document	1,10-15, 20,22-27
A	WO 97 18304 A (MASSACHUSETTS INST TECHNOLOGY ;UNIV PENNSYLVANIA (US); UNIV TEXAS) 22 May 1997 (1997-05-22) the whole document	1-34

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	MURAKAMI, M., ET AL.: "Distinction in the mode of receptor-mediated endocytosis between high density lipoprotein and acetylated high density lipoprotein: evidence for high density lipoprotein receptor-mediated cholesterol transfer" THE JOURNAL OF BIOCHEMISTRY, vol. 101, 1987, pages 729-741, XP002117461 the whole document	1-34

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INTERNATIONAL SEARCH REPORT

[redacted]ation on patent family members

[redacted]national Application No
PCT/US 99/10619

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		DK 94091 A	17-05-1991
		EP 0444154 A	04-09-1991
WO 9718304 A	22-05-1997	US 5925333 A	20-07-1999
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		CA 2240192 A	22-05-1997
		EP 0862625 A	09-09-1998